REMARKS

Claims 28-57, 59, 61-67 and 70-82 are all the claims pending in the application.

Entry of the instant Response is respectfully requested.

I. Claim Rejections under 35 U.S.C. §103

A. At paragraph 7 of the Office Action, claims 28-45 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lakowicz (WO 99/36779, issued July 22, 1999) in view of Kummerlen (Molecular Physics, 1993).

The Examiner states that Lakowicz discloses an assay in which a metal-ligand complex is brought into proximity with a sample containing an analyte of interest. The mixture is electromagnetically irradiated and if light is emitted, the analyte of interest is identified as being present in the sample. The Examiner further states that the metal-ligand complex is conjugated to human serum albumin, considered to be a second biomolecule that is covalently linked to the metal. The ligand is noted to be carbon monoxide, thus suggesting that the metal particle is coated with an oxide as recited in claim 32. The Examiner states that Lakowicz further discloses that the assay may be used to quantify an analyte where a first and second binding partner is added to the sample, and the first binding partner competes with the analyte for binding to the second binding partner. One of the binding partners is labeled with the metal ligand complex, and the other is labeled with a photoluminescent energy transfer acceptor, and when the two are brought into proximity, a detectable change in luminescence can be detected.

The Examiner notes that Lakowicz does not teach arrangement of metal particles on a solid support. The Examiner states that Kummerlen discloses enhancement of fluorescence intensity wherein a dye film is brought into proximity of the "island film support." The Examiner explains that the situation of a silver island film consists of many individual metal spheroids.

The Examiner concludes that one of ordinary skill in the art would have been motivated to apply the one or more metal particles of Lakowicz on a solid support to make the system as claimed because, as taught by Kummerlen, the silver island film is a suitable model for the effective dielectric constant.

While Applicants respectfully traverse the Examiner's position for the following reasons, Applicants first provide some general comments summarizing the basic nature of the invention recited in claims 28-45, and the disclosures of the cited art.

Claims 28-45 recite a system that can be used to detect the presence of a biomolecule in a sample based on the intrinsic fluorescence of the biomolecule. Prior to the instant invention, while it was known that biomolecules would fluoresce when exposed to electromagnetic radiation, the amount of fluorescence was so low as to be barely detectable. The invention recited in claims 28-45 is a system that takes advantage of the novel finding by Applicants that placing biomolecules in close proximity to metal has the unexpected result of increasing the intrinsic fluorescence of the biomolecule. The increased intrinsic fluorescence is sufficient to be detected using readily available detection means. Importantly, the novel system of the present invention does not require the use of an extrinsic fluorophore in order to detect the biomolecule in the sample. Indeed, the use of an extrinsic fluorophore is specifically disclaimed in claims 28-45.

In contrast, Lakowicz (WO 99/36779) cited by the Examiner teaches a superior probe (metal-ligand complex) for use in detecting the presence of an analyte of interest in a sample. The system of Lakowicz relies on the detection of light emitted by the probe. Thus, in contrast to the system of claims 28-45 that measures the fluorescence emission of the biomolecule itself, the system of Lakowicz is based on the detection of emissions from the extrinsic probe and not the analyte in the sample.

Kummerlen teaches improvement of fluorescent emission from dye molecules in a layer on a silver island film. The experimental data provided by Kummerlen demonstrates one can advantageously affect the emission spectra of organic dye molecules by layering the dye molecules over a silver island film.

In order for the Examiner to maintain a rejection under 35 U.S.C. §103, the Examiner must show (1) that the cited references teach each and every element of the claim, (2) that there is a suggestion or motivation in the cited references or the general knowledge of the art to modify the references to make the claimed invention, and (3) that there is a reasonable

expectation of success that the modification will yield the claimed subject matter. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See also MPEP §2142.

A rejection under 35 U.S.C. §103 may be traversed by arguing that the Examiner has not established one or more of the elements of a *prima facie* showing of obviousness.

In the instant application, the Examiner has not established that the combination of Lakowicz and Kummerlen teaches each and every element of the rejected claims. In particular, and as mentioned above, Applicants note that the instant claims specifically disclaim the inclusion of an extrinsic fluorescent marker as a part of the claimed system (claim 28). Paragraph 62 of the pending application (page 11) defines extrinsic fluorescent markers as fluorophores bound to another molecule. Extrinsic fluorophores are specifically defined to include "metal-ligand complexes" (page 11, line 23). As noted by the Examiner in the instant Office Action, the assay system of Lakowicz is based on the use of "metal-ligand complexes." As metal-ligand complexes are taught as extrinsic fluorophores in the instant application, and as rejected claims 28-45 specifically disclaim extrinsic fluorophores, Lakowicz does not teach this element (lack of an extrinsic fluorescent marker) of the rejected claims.

The extrinsic fluorophores of the present application are also specifically defined (paragraph 62) to include sulfonyl chloride containing moieties, iodoacetamide moieties, hydroxysuccinimide moieties and isothiocyanante moieties (lines 11-19). The metal-ligand complexes described in Lakowicz are described as including ligands substituted with such groups (page 11, line 31, through page 12, line 6). Thus, again, Lakowicz teaches the use of an extrinsic fluorophore that is specifically disclaimed in the rejected claims of the pending application.

Applicants also note that Kummerlen teaches the use of a dye molecule, namely Rhodamine 6G (page 1033, second full paragraph). Rhodamine is included among the list of extrinsic fluorescent markers in paragraph 62 of the present invention (line 19).

Accordingly, as both Lakowicz and Kummerlen require the use of extrinsic fluorescent markers, and as rejected claims 28-45 disclaim the use of extrinsic fluorescent markers, the combination of Lakowicz and Kummerlen does not teach each and every element of claims 28-45 and as such, the Examiner has not established a *prima facie* showing of obviousness.

Applicants also note that there would have been no motivation or suggestion to combine the teachings of Lakowicz and Kummerlen. In particular, there would have been no motivation for the skilled artisan to use the silver island film of Kummerlen in conjunction with the assay system of Lakowicz.

Kummerlen teaches improvement of fluorescent emission from dye molecules in a layer on a silver island film. The experimental data provided by Kummerlen demonstrates one can advantageously affect the emission spectra of organic dye molecules by layering the dye molecules over a silver island film. In contrast, Lakowicz teaches the enhancement of emissions from metal particles themselves. There is no teaching or suggestion in Kummerlen to use a silver island film (e.g., a metal layer) in conjunction with the metal-ligand complexes of Lakowicz. Indeed, as the assay system of Lakowicz already makes use of the properties of metal (in the metal-ligand complexes), it is clear that there would have been no reason to use a second metal (i.e., the silver island film of Kummerlen) in the assay system of Lakowicz.

In addition, the metal in the metal-ligand complexes of Lakowicz is ionized, whereas the metal in the films of Kummerlen is metallic metal. Metallic metal causes the enhancement effects of Kummerlen. Further, the metal in the metal-ligand complexes of Lakowicz is part of a single molecule, whereas the metal in the particles of Kummerlen is part of a larger aggregate of neutral atoms.

Applicants further note that the skilled artisan would not have been motivated to prepare the metal-ligand complexes of Lakowicz in a form where the metal is affixed to a solid support. As noted by the Examiner, the metal-ligand complexes of Lakowicz are used in DPPG-labeled vesicles or conjugated to proteins, such as HSA. The complexes are thus used as dispersible probes to be added to a sample.

Moreover, the skilled artisan would not have been motivated to use the silver island film of Kummerlen in an assay system with a biomolecule (as recited in claim 28). While the silver island film of Kummerlen was shown to have an effect on the fluorescence of a dye molecule, there is no suggestion that the silver island film of Kummerlen would have had any effect on the fluorescence of a biomolecule.

Finally, Applicants note that the skilled artisan would not have had a reasonable expectation of success in arriving at the invention recited in claims 28-45 in view of the teachings of Lakowicz and Kummerlen. For the reasons described above, it is clear that the combination of Lakowicz and Kummerlen would have resulted in an assay system that uses an extrinsic fluorescent marker. As claims 28-45 specifically disclaim the use of such a marker, the skilled artisan would not have had a reasonable expectable of success in producing an assay system that could measure the intrinsic fluorescence of a biomolecule. Indeed, the fluorescence emitted by the metal in the metal-ligand complex of Lakowicz, and the fluorescence emitted by the rhodamine dye of Kummerlen would overshadow the intrinsic fluorescence of a biomolecule

As the Examiner has not established a *prima facie* showing of obviousness with respect to claims 28-45, Applicants respectfully request reconsideration and withdrawal of this rejection.

B. At paragraph 8 of the Office Action, claims 46-57, 59, 61-67 and 70-82 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lakowicz in view of Kneipp (Curr. Science, 1999).

The Examiner refers to her earlier comments regarding Lakowicz, and also notes that Lakowicz does not teach the use of metal particles selected from the group consisting of rhodium, palladium, silver, iridium, platinum and gold. The Examiner states that this deficiency is cured by Kneipp, which teaches the use of both colloidal gold clusters and colloidal silver clusters. The Examiner concludes that one of ordinary skill in the art would have been motivated to use silver or gold as metal particles in the system of Lakowicz, as taught by Kneipp, because colloidal gold clusters are used as a substrate for highly sensitive SERS which can provide an enhancement level sufficient for Raman single molecule detection.

Applicants respectfully traverse the Examiner's position. In particular, there would have been no motivation to combine the teachings of Lakowicz and Kneipp to arrive at the present invention.

Applicants note that there is a fundamental difference between the Raman scattering of Kneipp and the fluorescence utilized in the present application. Raman scattering occurs when a laser photon strikes a molecule, loses energy and causes the molecule to vibrate. The result is

that the photon bounces off of the molecule at a lower energy state than it had prior to contacting the molecule. Specifically, the photon strikes the molecule at a specified wavelength and bounces off of the molecule at a higher wavelength. In contrast, fluorescence results from a molecule's complete absorption of an excitation photon, the excitation of the molecule, and the subsequent emission of that photon. For this process to take place, the excitation photon must provide a sufficient amount of energy to the molecule in order for fluorescence to take place. In view of this fundamental difference, Raman scattering can result from any frequency of the incident light, whereas fluorescence requires a minimum frequency (usually a frequency that corresponds to a wavelength within the UV range).

Kneipp teaches the use of colloidal gold clusters and colloidal silver clusters to provide ideal enhancement levels at near-infrared excitation (page 918, col. 1, lines 1-3). The near infrared range is from 750 nm to 1,400 nm. In contrast, the present invention uses electromagnetic radiation within the ultraviolet and visible light ranges, i.e., from 280 nm - 295 nm, and 520 nm, respectively (see, e.g., claims 42, 43, 64, 65, 78 and 79).

The skilled artisan reviewing Kneipp would not have been motivated to use the colloidal gold clusters and colloidal silver clusters in the assay system of Lakowicz. First, the fundamental basis of the underlying physics of Raman scattering and fluorescence is completely different. As such, the skilled artisan would not have expected that silver and gold of Kneipp's SERS system could be used in an assay system based on the detection on fluorescence. Second, as specifically taught in Kneipp, the silver and gold clusters are used to provide enhancement of SERS at using near infrared light. Such a wavelength of light is not used in the assay system of the present invention (which uses ultraviolet and visible light). Because the beneficial effect of gold and silver metal in Kneipp is directly related to the wavelength of light striking the metal particles, the skilled artisan would not have been motivated to use the gold and silver clusters of Kneipp in the assay system of Lakowicz.

Further, the skilled artisan would not have had a reasonable expectation of success in combining the teachings of Lakowicz and Kneipp. As noted above, the silver and gold of Kneipp was used to enhance SERS when using near infrared wavelengths of light. In contrast,

Lakowicz describes the detection of fluorescence using ultraviolet and visible wavelengths of light to measure the fluorescence of a biomolecule. In view of the completely different assay systems, the skilled artisan would not have had a reasonable expectation that the silver and gold clusters of Kneipp could be used in the assay system of Lakowicz.

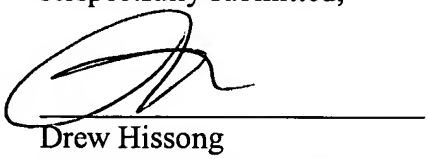
Accordingly, the Examiner has not established a *prima facie* showing of obviousness with regard to claims 46-57, 59, 61-67 and 70-82, and Applicants respectfully request reconsideration and withdrawal of this rejection.

II. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Drew Hissong
Registration No. 44,765

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